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Biological or relational screening for liver disease?

To the Editor:

As a member of the "discordantist" family [1] I agree with Dr. Poynard's proposal of non invasive methods as a first line investigation for assessment of liver fibrosis [2]. However, from a public health and financial point of view, a "sequentialist" attitude in case of liver disease could probably be a more preferable recommendation.

Another aspect of Dr. Poynard's proposal to screen general population for liver fibrosis by using biomarkers is very questionable:

It seems more satisfactory to screen, at first line, the etiological factors, than for their liver consequences. As pointed in Dr. Poynard's study [3], in a general population, almost 9 out of 10 cases of confirmed liver fibrosis can be attributed to metabolic causes (alcohol and more importantly non alcoholic fatty liver disease). Instead of considering new biological tests for screening, it is more important to teach and promote screening, by general practitioners and other first line health professionals, for premature mortality risk factors: overweight, obesity, and sedentarity related metabolic syndrome, at risk or excessive alcohol consumption, and tobacco, without forgetting risk factors for viral hepatitis B and C. Such a screening should be more efficient from a global individual and public health point of view: it is possible to have metabolic syndrome or alcohol excessive intake without confirmed liver fibrosis but (more frequently!) with other somatic complications (especially cardiovascular and/or tumoral diseases).

The use of biomarkers without screening for overweight, obesity, sedentarity, at risk or excessive alcohol consumption, tobacco, or viral hepatitis B and C risk factors will be nonsense: if evaluation for confirmed liver fibrosis by biomarkers was positive, screening for these factors would be a secondary necessity. However, in case of confirmed liver fibrosis excluded by biomarkers, it will be necessary to screen for the same risk factors. So what is the interest to test the general population by biomarkers, instead of only screening for suspected liver fibrosis in patients with risk factors?

At this state of the discussion, a frequent comment is: "you could be right but after the recognition of risk factors, what do you propose?" suggesting a negative answer. But the same answer is also possible (except in case of cirrhosis) after biomarkers screening for metabolic liver disease! And in fact this comment is wrong: a lot of Evidence Based Medicine (EBM) behavioral and cognitive data has been published, showing significant and durable results in weight loss and physical activity in patients with overweight, obesity, and diabetes. These results have been confirmed recently for patients with non alcoholic steatohepatitis [4]. It is not the place to develop more extensively this aspect, but just one example: a very recent paper showed a strong association between practitioners saying clearly to the patient the diagnosis of obesity, its importance for health, and the obtention of significant and durable weight loss [5]. We have to look carefully not only for EBM data about biological and morphological tests, drug, or surgical treatment but also for behavioral and cognitive EBM data. Scientific rigour should not accept fragmentation and only partially taking into account available data.

Conflict of interest

The author declared that he does not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Pre-treatment prediction of response to pegylated-interferon plus ribavarin for chronic hepatitis C using RVR

To the Editor:

We read with interest the paper of Kurosaki and colleagues [1] and applaud their use of data mining to develop a decision tree to predict HCV treatment outcomes. We agree with them that prediction of treatment outcome is very important in the process of physician and patient making a decision to commence treat-

ment for HCV infection, especially genotype 1. This prevents futile therapy in patients with little chance of cure, and the decision tree presentation also offers the opportunity for patients to be actively involved in setting the level of futility. Thus, they have developed a clinically useful negative predictive tool. However, with the advent of protease inhibitors and the greatly increased cost of these therapies, identifying the patients who would be cured with standard of care, a positive predictive tool is now even more important, if we are to reduce the implementation costs of these new drugs to maximise benefit for all patients. Clearly a pre-treatment prediction tool would be useful, but not essential, if the decision to treat has been made and the tool is to be used to individualise therapy. Some of the new therapies propose a 4-week run in therapy with interferon and ribavirin before starting a protease inhibitor. There being arguments for using this regimen to reduce risk of viral resistance in all therapies. Thus a tool incorporating a rapid virological response (RVR) at 4 weeks [2] would still be useful if it had a significant positive predictive value. We still have a very incomplete understanding of the factors that determine interferon sensitivity. Polymorphisms around the *IL28* gene are clearly important but do not account for the whole variance in interferon response seen in patients, in terms of SVR. The analysis of this polymorphism has not been established as a routine test outside a research setting, so its availability and reliability is limited at present. An early response time point, such as a 4 week RVR, dynamically tests a given patient and virus' interferon sensitivity, and provides a global test of response factors including the influence of *IL28B* polymorphisms and the ISDR mutations in the HCV virus. The ISDR mutations in HCV are associated with host hepatic steatosis and lipid dysregulation, this has been correlated with elevation of GGT. We, therefore, used the decision tree developed by Kurosaki and colleagues and substituted RVR for *IL28B* genotype and GGT for ISDR, to see if these commonly available measures changed the function of the tool as a positive predictor of SVR in therapy with interferon and ribavirin. We applied the decision tree tool to our consecutively treated cohort of 114 HCV genotype 1 patients for whom we had RVR data, as demonstrated in Fig. 1. The cohort

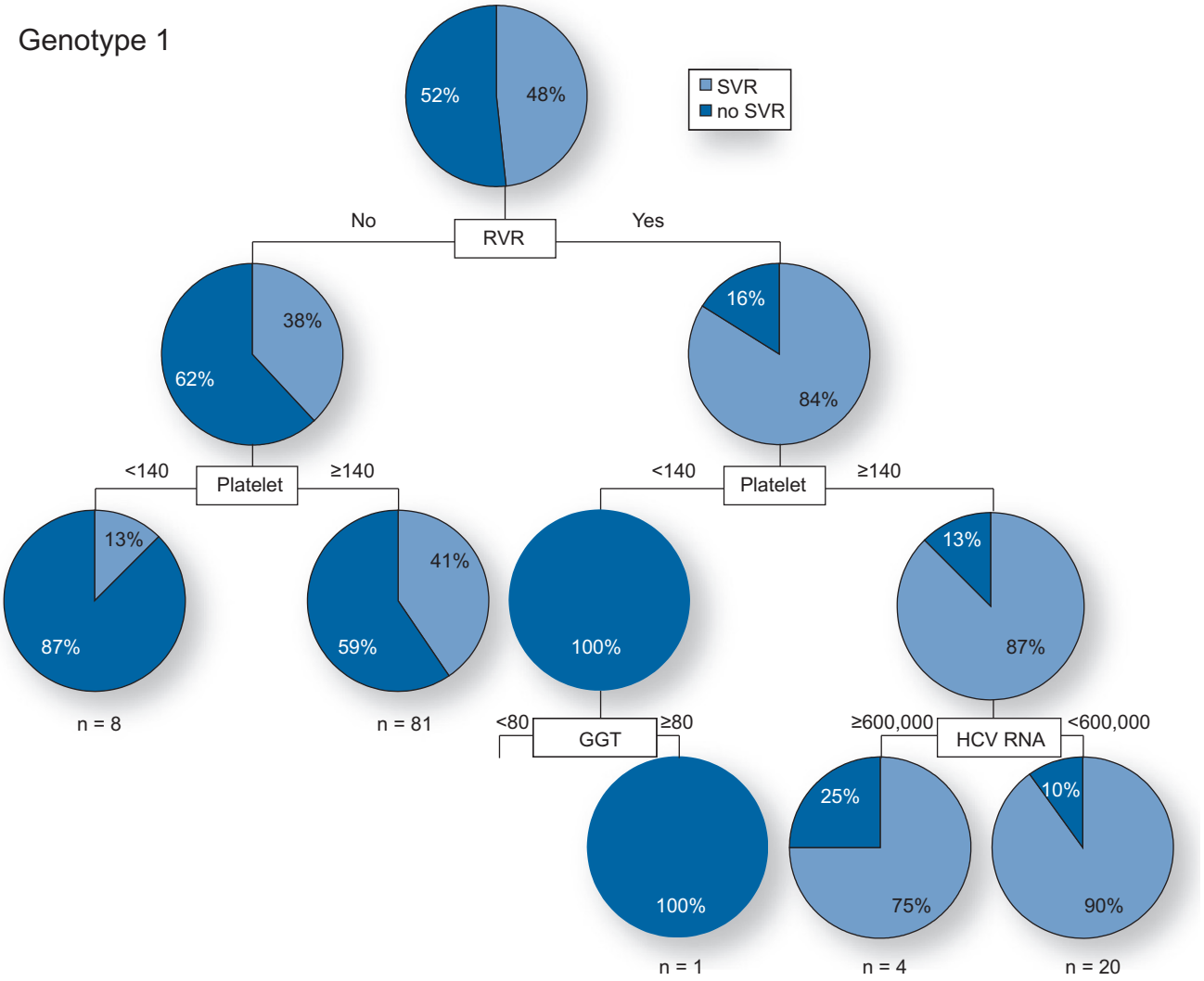

Fig. 1. 17.5% of the cohort were shown to have achieved a RVR with normal platelets and a low viral load. 90% of these patients were shown to achieve a SVR with standard of care combination therapy.

is predominantly Caucasian, male (75%), younger (mean age 43), and has a higher proportion of current and former drug users (68%), than the Japanese cohort. We also had a lower prevalence of cirrhosis (11%). These differences meant that some parts of the decision tree were under populated. However, the tree was able to identify a subgroup of patients who achieved a RVR, with normal platelets and a low viral load, representing 17.5% of the cohort who had a 90% chance of achieving a SVR with standard of care combination therapy. This level of SVR means it is much more cost-effective to treat such patients with standard peginterferon and ribavirin than to add a protease inhibitor as first line therapy. Equally there is currently no evidence that the protease inhibitors will improve the outcome in this patient group. We congratulate Kurosaki and colleagues on an easy to use tool that helps patients and physicians make decisions on starting therapy and that with minor modifications may make the impact of the introduction of protease inhibitors much more cost effective.

Conflict of interest

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Reply to: "Pre-treatment prediction of response to pegylated-interferon plus ribavarin for chronic hepatitis C using RVR"

Decision model incorporating *IL28B* genotype and ISDR could identify patients with high probability of SVR among patients who failed to achieve RVR

To the Editor:

We appreciate the interest of Dr. Wahed in our article recently published in the *Journal of Hepatology* [1]. We were impressed of their validation of our prediction model by substituting rapid virological response (RVR) for *IL28B* genotype (modified model) [2]. Wahed *et al.* showed that among patients with RVR, those with high platelet counts ($\geqslant 140 \times 10^9$/L), and low HCV RNA (<600,000 IU/ml)) had 90% chance of sustained virological response (SVR). Their results confirmed our finding that platelet count and pretreatment HCV RNA level are predictors of SVR, independently of early virological dynamics and showed that combination of these factors improved the prediction accuracy. However, according to their data, a modified model could not identify patients who have high chance of SVR among those who failed to achieve RVR.

In a study by Thompson *et al.* [3], RVR was correlated with the *IL28B* genotype and was a strong predictor of SVR regardless of *IL28B* genotype. On the other hand, the major *IL28B* genotype (CC at rs12979860) was associated with a higher rate of SVR (among Caucasians, 66% (*IL28B* major genotype) *vs.* 31% (*IL28B* minor hetero-genotype) and 24% (*IL28B* minor genotype)) among patients who failed to achieve RVR. There were similar findings in our cohort, where patients with RVR had a high rate of SVR independent of *IL28B* genotype (97% for *IL28B* major type *vs.* 100% for *IL28B* minor type) but among non-RVR patients, the *IL28B* major genotype was associated with significantly higher rate of SVR (45% for *IL28B* major genotype *vs.* 12% for *IL28B* minor genotype). Collectively, *IL28B* genotype has a significant predictive power even after virological response at week 4 of therapy was determined. This means that RVR is associated with *IL28B* genotype but RVR could not entirely replace *IL28B* genotype for the accurate prediction of SVR. In order to assess if our model still has the power to predict SVR after virological response at week 4 of therapy was determined, we modified our predictive model by adding RVR as a first splitting variable and applied the data of our cohort. As a result, among patients who failed to achieve RVR in our cohort, patients with *IL28B* major genotype who had (1) high platelet counts ($\geqslant 140 \times 10^9$/L), and low HCV RNA (<600,000 IU/ml) had 87% chance of SVR, (2) high platelet counts ($\geqslant 140 \times 10^9$/L), and high HCV RNA ($\geqslant$600,000 IU/ml) had 60% chance of SVR, and (3) low platelet counts ($<140 \times 10^9$/L), and more than 2 mutations in interferon sensitivity determining region (ISDR) [4] had 69% chance of SVR (Fig. 1). Patients who fall into these three groups constitute 39% of non-RVR patients. Thus, our predictive model could determine patients with high probability of SVR even after virological response at week 4 of therapy was determined.

We fully agree with Dr. Wahed that it is important to identify the patients who would be cured with current standard of